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Original Article

Normothermic regional and ex situ perfusion reduces postreperfusion syndrome in donation after circulatory death liver transplantation: A retrospective comparative study

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ABSTRACT

In controlled donation after circulatory death (DCD) liver transplantation, ischemia-reperfusion injury is linked to postreperfusion syndrome (PRS), acute kidney injury (AKI), and early allograft dysfunction. Normothermic regional perfusion (NRP) and normothermic machine perfusion (NMP) are techniques that mitigate ischemic injury and associated complications. In this single-center retrospective study, we compared early transplant outcomes of DCD livers undergoing direct procurement (DP) and static cold storage (SCS) (DCD-DP-SCS), NRP procurement with SCS (DCD-NRP-SCS), or DP with NMP (DCD-DP-NMP). Two hundred thirty-eight DCD liver recipients were evaluated, comprising 59 DCD-DP-SCS, 101 DCD-NRP-SCS, and 78 DCD-DP-NMP. Overall, the PRS incidence was 19%. DCD-DP-SCS had a higher incidence of PRS (37%; $P < .001$), AKI stage ≥ 2 (47%; $P = .033$), and an increased model for early allograft function score ($P < .001$). In adjusted multivariate analysis, recipient age (odds ratio [OR] 1.10, 95% CI 1.05-1.17; $P < 0.001$),

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; CIT, cold ischemia time; DBD, donation after brain death; DCD, donation after circulatory death; DP, direct procurement; EAD, early allograft dysfunction; fWIT, functional warm ischemia time; ICU, intensive care unit; INR, international normalized ratio; IR, ischemia-reperfusion; MEAF, model for early allograft function; MELD, model for end-stage liver disease; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; PNF, primary nonfunction; POD, postoperative day; PRS, postreperfusion syndrome; SCS, static cold storage; UW, University of Wisconsin; ΔK, plasma potassium change (increase) at reperfusion.

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and normothermic perfusion (DCD-NRP-SCS: OR 0.16, 95% CI 0.06-0.39; $P < .001$; DCD-DP-NMP: OR 0.38, 95% CI 0.15-0.91; $P = .032$) were significant predictors of PRS, which itself was associated with worse 5-year transplant survival (graft survival non–censored-to-death; Hazard ratio (HR) 2.9, 95% CI 1.3-6.7; $P = .012$). Compared to SCS alone, the use of either NRP or NMP significantly reduced the incidence of PRS and AKI with better early graft function.

1. Introduction

Liver transplantation is the definitive treatment for most patients with end-stage liver disease, but a shortage of organs from donors fulfilling criteria for brain death continues to limit transplant activity across the globe, resulting in pretransplant mortality as high as 10% to 20%.[1,2] This has fostered the development of new techniques of organ preservation to allow the use of organs from a much larger group of potential donors: those dying following withdrawal of cardio-respiratory support (donation after circulatory death [DCD]).

Unlike those in donation after brain death (DBD), when circulation remains intact until cold perfusion, organs recovered after circulatory death are unavoidably hypoperfused at near-normal body temperature before the circulatory arrest, and for a period afterward. This causes rapid depletion of energy substrates, accumulation of lactate, and disruption of transmembrane ionic pumps, a condition defined as "warm ischemia."[3,4] As a result, despite the use of long-established preservation fluids for static cold storage (SCS), they are at higher risk of ischemia-reperfusion (IR) injury. This manifests in the perioperative period as post-reperfusion syndrome (PRS), acute kidney injury (AKI), and early allograft dysfunction (EAD), all linked to a longer hospital stay and reduced posttransplant survival.[5-7]

In situ normothermic regional perfusion (NRP), in which abdominal organs are perfused prior to cold perfusion and removal, and ex situ normothermic machine perfusion (NMP), which follows a period of SCS, are 2 novel techniques that appear to mitigate IR injury and associated complications.[8-11] We have extensive experience in using both techniques for DCD donor livers and this study examines whether these normothermic techniques are associated with a reduction in the clinical manifestations of reperfusion injury, such as PRS, AKI, and EAD, compared to livers preserved by SCS.

2. Patients and methods

2.1. Data collection

This single-center, retrospective study was performed after approval by the University of Cambridge Human Biology Research Ethics Committee (Ref no: HBREC.2020.23) as a service evaluation. Data were collected from electronic patient records (Epic Systems Corporation, Wisconsin, USA) and a prospectively maintained transplant perfusion database in accordance with the Interventional Procedures Guidance IPG636 by the National Institute for Health and Care Excellence (NICE).[12] We reviewed consecutive adult recipients (aged >18 years) of controlled DCD transplants (Maastricht category III and IV) from January 1, 2015, to December 31, 2022, and defined into 3 groups according to the procurement and preservation technique: DCD-DP-SCS (direct procurement [DP] followed by SCS), DCD-NRP-SCS (normothermic in situ regional perfusion followed by SCS) and DCD-DP-NMP (DP and SCS followed by normothermic ex situ machine perfusion at recipient hospital).[13] We excluded recipients with sequential NRP-NMP livers and those requiring veno-venous bypass during the transplant. The study (Supplementary material) followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

DCD donor livers underwent NRP if within our region, or within easy traveling distance and a team capable of undertaking NRP was available. They underwent NMP when recovered by another recovery team and sent to us in SCS for transplant. DCD-DP-SCS livers were allocated to recipients with short predicted explant times (low medical and/or surgical risk). There was no bias in the selection of recipients for NRP or NMP, which were considered to be as good as DBD organs if passing viability criteria. Our center stopped using DCD-DP-SCS livers for transplantation in January 2019.

The US Donor Risk Index was calculated as a surrogate measure of donor liver quality.[14] Functional warm ischemia time (fWIT) was defined as the time interval between systolic pressure <50 mmHg and the start of either in situ normothermic perfusion or cold in situ flush.[15] Cold ischemia time (CIT) was defined as the time interval between cold in situ aortic flush with University of Wisconsin (UW) preservation fluid and reperfusion, either in the recipient or on ex situ NMP.

The United Kingdom end-stage liver disease[16] score and model for end-stage liver disease (MELD) score were calculated to indicate the severity of recipient liver disease.[17] Perioperative outcomes included the presence of PRS, plasma potassium change (increase) at reperfusion (ΔK), lactate metabolism in the first 8 hours after reperfusion, intraoperative transfusion requirement, perioperative AKI, EAD, and primary nonfunction (PNF). Total length of intensive care unit (ICU), hospital stay, and 5-year transplant survival (graft survival noncensored for death) were also included. All the livers had a minimum of 12 months of follow-up.

The primary endpoint of the study was the incidence of PRS, defined as a decrease in mean arterial pressure >30% below the baseline value in the 5 minutes before reperfusion, for at least 1 minute during the first 5 minutes after reperfusion (unclamping of

hepatic hilum).[18,19] Vasopressor bolus (metaraminol or epinephrine) administered within the first 5 minutes postreperfusion was also recorded separately. ΔK was calculated from arterial blood gas samples at 5 to 10 minutes prereperfusion and immediately postreperfusion. AKI was defined as ≥stage 2 of the Kidney Disease Improving Global Outcomes criteria (≥2.0 times baseline creatinine or initiation of renal replacement therapy within the first 7 days after transplant).[20] Early allograft function was quantified using the model for early allograft function (MEAF) score, which is based on the maximum alanine aminotransferase (ALT) value during the first 3 postoperative days (PODs) (ALTmax.3POD), the maximum international normalized ratio (INR) during the first 3 PODs (INRmax.3POD) and the bilirubin value on day 3 after liver transplantation (bilirubin 3POD).[21] PNF was defined as graft loss or death within 7 days posttransplant excluding hepatic artery thrombosis, technical issues, or acute rejection.

2.2. Anesthetic management

Anesthetic management followed the standard protocol at our institution, typically including intravenous induction with propofol followed by maintenance with an inhalation agent, remifentanil, and atracurium. All patients had invasive radial arterial pressure monitoring, a multilumen central venous catheter, and a pulmonary artery catheter introducer. Additional large bore central venous access was used if veno-venous bypass was required. Cardiovascular monitoring with transesophageal echocardiography was at the discretion of the attending anesthesiologist. Arterial blood gas samples were analyzed at predetermined intervals, typically at each hour from the time of induction, every 30 to 40 mins during the anhepatic phase, 30 to 60 seconds after reperfusion, at unclamping of the hepatic artery, and hourly until closure. Plasma potassium values above 5 mmol/L during the dissection or anhepatic phase were treated with a glucose/insulin infusion. A metaraminol or norepinephrine infusion was used to maintain mean arterial pressure within 20% to 30% of baseline. Calcium chloride and bolus vasopressor were used as required at reperfusion. Postreperfusion vasoplegia was treated with boluses of metaraminol or epinephrine, and vasopressin infusion was considered for refractory hypotension. Red cell concentrates were transfused to maintain a hemoglobin level of >70 to 80 g/L. Fresh frozen plasma, platelets, and cryoprecipitate were used as guided by thromboelastography and assessment of the surgical field. Tranexamic acid was used in the presence of fibrinolysis as indicated by thromboelastography. Anesthetic charts were reviewed by 2 consultant anesthetists (A.P. and V.K.) independently.

2.3. Organ preservation and surgical technique

DCD recovery followed a standard UK protocol with no donor intervention allowed before the declaration of death 5 minutes after circulatory arrest.[22] UW preservation solution (Belzer UW, Bridge to Life, London, UK) was used for dual aortic and portal perfusion in addition to topical ice for rapid cooling. SCS, which is still the standard in the UK, involved organ storage and transportation in a box filled with slushed ice. We have previously described the technical details of NMP and NRP.[23-28] There is national guidance on NRP in the UK with a steering group and periodic reviews.[29] NMP was performed at the recipient center after transportation in cold storage as a back-to-base model.[30] NMP was undertaken using the OrganOx metra device, and NRP using the Maquet Cardiohelp and continued for 2 hours. No liver underwent hypothermic machine perfusion.

The standard implantation technique included either classical or cava-sparing modified piggyback caval anastomosis. All livers were reperfused on the portal vein. Before reperfusion and after caval anastomosis, the livers were flushed with succinylated gelatin (Gelofusine, BBraun) to flush out any residual UW solution and warm the liver. The biliary anastomosis was routinely duct-to-duct, with Roux-en-Y hepaticojejunostomy for recipients with primary sclerosing cholangitis, duct size discrepancy, or prior transplant. The degree of macrovesicular steatosis was assessed in postreperfusion liver biopsy. It was divided into 2 groups based on a cut-off of 30% steatosis.

2.4. Statistical analysis

Continuous variables are expressed as median (IQR) and categorical variables as frequency and percentage. Comparison of continuous variables was performed using Kruskal-Wallis with Dunn's test for multiple pairwise comparisons for 3 groups (DCD-DP-SCS vs DCD-NRP-SCS vs DCD-DP-NMP) and the Mann-Whitney test for 2 groups (PRS+ vs PRS–). Categorical variables were compared using chi-square or Fisher exact tests as appropriate. Potential predictors of PRS, selected on clinical grounds and including liver treatment method, were entered a priori into a logistic regression model. Covariates considered in the multivariate analyses were liver treatment method (DCD-DP-SCS reference), donor age, CIT, liver steatosis>30%, recipient age, and MELD score. All variable values were included, none transformed and interaction terms were omitted. Appropriate consideration was given to study group numbers, outcome event frequencies, and model degrees of freedom. Transplant survival, estimated using the Kaplan-Meier method, was compared between groups by log-rank analysis. All variables with $P < .05$ were considered statistically significant. Statistical analysis was performed with Prism version 10.1.1 (GraphPad Software, San Diego, California, USA).

3. Results

During the study period, 278 patients were transplanted with controlled DCD livers. After the exclusion of 31 recipients receiving sequential NRP and NMP grafts, 8 recipients requiring veno-venous bypass during transplant and 1 with incomplete intraoperative data, 59 recipients with DCD-DP-SCS livers, 101 with DCD-NRP-SCS livers, and 78 with DCD-DP-NMP livers were included in the analysis. Of NRP donors, 14 had thoracoabdominal NRP (TA-NRP), 17 had DP of heart/lung with abdominal NRP (DP-NRP); all others had abdominal NRP (A-NRP) alone.

3.1. Donor and recipient characteristics

Median donor age and the United States Donor Risk Index were comparable between the groups (Table 1). CIT was longer in the DCD-DP-SCS group ($P = .007$) and median fWIT was longer in the DCD-NRP-SCS group (SCS 12 minutes, NRP 17 minutes, NMP 12 minutes; $P < .001$). Longer fWIT in the DCD-NRP-SCS group was expected, reflecting additional time required to establish the donor on the extracorporeal circuit.

A greater proportion of male (assigned male at birth) recipients received normothermic livers (DCD-DP-SCS 53%, DCD-NRP-SCS 72%, DCD-DP-NMP 72%; $P = .012$), but there were

Table 1
Donor and recipient characteristics.

Parameter	Liver treatment method				Presence of PRS		
	DCD-DP-SCS (n = 59)	DCD-NRP-SCS (n = 101)	DCD-DP-NMP (n = 78)	*P* value	PRS− (n = 193)	PRS+ (n = 45)	*P* value
Donor age, y	50 (36-58)	55 (42-60)	46 (28-59)	.055	51 (35-59)	55 (42-62)	.175
US DRI	2.5 (2.0-3.0)	2.3 (2.1-2.5)	2.4 (2.0-2.8)	.186	2.3 (2.0-2.7)	2.5 (2.1-3.0)	.107
CIT, min	438 (392-491)	422 (367-500)	401 (346-447)	.007	411 (365-482)	442 (382-515)	.102
fWIT, min	12 (10-14)	17 (14-19)	12 (11-14)	<.001	14 (11-17)	13 (11-15)	.108
Recipient age, y	56 (49-62)	57 (48-62)	56 (49-61)	.943	56 (47-62)	60 (56-66)	<.001
Male recipient	31 (53%)	73 (72%)	56 (72%)	.012	124 (64%)	36 (80%)	.035
Recipient BMI, kg/m^2	26.6 (23.4-29.0)	28.6 (23.9-33.9)	28.1 (23.9-33.6)	.077	28.2 (23.7-33.1)	27.5 (24.2-31.3)	.593
MELD	16 (13-20)	14 (10-18)	14 (11-16)	.135	14 (11-18)	16 (11-18)	.605
UKELD	55 (53-58)	55 (51-58)	53 (51-57)	.132	54 (51-58)	55 (52-59)	.472
Indication for liver transplant							
Alcohol-related liver disease	18 (31%)	32 (32%)	22 (28%)	.877	59 (31%)	13 (29%)	.825
MASLD	8 (14%)	23 (23%)	17 (22%)	.155	39 (20%)	9 (20%)	.975
Primary sclerosing cholangitis	9 (15%)	15 (15%)	7 (9%)	.945	27 (14%)	4 (9%)	.360
Primary biliary cholangitis	10 (17%)	4 (4%)	4 (5%)	.005	13 (7%)	5 (11%)	.317
Hepatitis C cirrhosis	9 (15%)	7 (7%)	12 (15%)	.090	24 (12%)	4 (9%)	.506
Retransplant	1 (2%)	7 (7%)	3 (4%)	.143	9 (5%)	2 (4%)	.949
Others	4 (7%)	13 (13%)	13 (17%)	.228	22 (11%)	8 (18%)	.246
Hepatocellular carcinoma	13 (22%)	26 (26%)	21 (27%)	.798	53 (28%)	7 (16%)	.127
Macrovesicular steatosis[a] >30%	2 (4%)	4 (4%)	1 (1%)	.424	4 (2%)	3 (7%)	.156
Liver treatment method							
DCD-DP-SCS	-	-	-	-	37 (19%)	22 (49%)	<.001
DCD-NRP-SCS					90 (47%)	11 (24%)	
DCD-DP-NMP					66 (34%)	12 (27%)	

Data presented as median (IQR) or number (%).
BMI, body mass index; CIT, cold ischemia time; DCD, donation after circulatory death; DP, direct procurement; fWIT, functional warm ischemia time (systolic pressure <50 mmHg to in situ perfusion); MASLD, metabolic dysfunction–associated steatotic liver disease; MELD, model for end-stage liver disease; NMP, ex situ normothermic machine perfusion; NRP, in situ normothermic regional perfusion; PRS, postreperfusion syndrome; SCS, static cold storage; UKELD, United Kingdom model for end-stage liver disease; US DRI, US Donor Risk Index.

[a] Missing liver biopsy SCS 3, NRP 8, NMP 4.

no differences in recipient age (years), BMI, MELD score, or United Kingdom end-stage liver disease score between the 3 groups. Recipient preoperative serum creatinine was higher in the DCD-NRP-SCS group (DCD-DP-SCS 63 μmol/L, DCD-NRP-SCS 73 μmol/L, DCD-DP-NMP 63 μmol/L; $P = .004$). Alcohol-related liver disease was the most common indication for transplantation in all the 3 groups. There were disproportionately more primary biliary cholangitis recipients in the DCD-DP-SCS group ($P = .005$). Retransplants predominantly received DCD-NRP-SCS grafts (DCD-DP-SCS 2%, DCD-NRP-SCS 7%, DCD-DP-NMP 4%). Higher recipient age ($P < .001$) and use of DCD-DP-SCS ($P < .001$) were significantly associated with PRS.

3.2. Intraoperative outcomes

The intraoperative outcomes are shown in Table 2. The DCD-DP-SCS group had a significantly higher incidence of PRS (DCD-DP-SCS 37%, DCD-NRP-SCS 11%, DCD-DP-NMP 15%; $P < .001$). In unadjusted analysis, the odds of developing PRS in DCD-DP-SCS preserved livers were 3 to 5 times higher compared to normothermic livers (DCD-DP-SCS vs DCD-NRP-SCS, odds ratio [OR] 4.9, 95% CI 2.2-11.4, $P < .001$; DCD-DP-SCS vs DCD-DP-NMP, OR 3.3, 95% CI 1.5-7.6, $P = .004$) and a greater proportion of patients in the DCD-DP-SCS group (81%) required bolus vasopressor administration during reperfusion to maintain hemodynamic stability ($P = .009$). Two recipients (3%) in the DCD-DP-SCS group suffered cardiac arrest after reperfusion requiring intraoperative cardiac massage; no recipient of the DCD-NRP-SCS or DCD-DP-NMP graft suffered a reperfusion cardiac arrest.

The prereperfusion plasma lactate was similar between the groups, but peak plasma lactate postreperfusion (first 8 hours after reperfusion) was significantly lower in the DCD-NRP-SCS group (Fig. 1A). Prereperfusion plasma potassium was similar between the groups, but the increase on reperfusion was significantly higher in the DCD-DP-SCS recipients (ΔK: median (IQR), mmol/L: DCD-DP-SCS 1.4, DCD-NRP-SCS 0.8, DCD-DP-NMP 0.6; $P < .001$, Fig. 1B). Prophylactic administration of insulin/dextrose to manage serum potassium was similar between the groups. Measured blood loss, blood products administered after reperfusion, and use of tranexamic acid were not significantly different between the groups.

3.3. AKI and early graft function

A greater proportion of patients in the DCD-DP-SCS group sustained Kidney Disease Improving Global Outcomes grade 2 or higher AKI (47%, $P = .033$), although there was no difference in renal replacement therapy in the first 7 PODs or median ICU stay (Table 3). The median peak ALT during the first 7 PODs was significantly higher after DCD-DP-SCS compared to both normothermic groups ($P < .001$). Likewise, the median MEAF score, quantifying early graft dysfunction, was significantly higher in the DCD-DP-SCS group ($P < .001$). Two livers in the DCD-DP-SCS group (3%) and one liver in the DCD-DP-NMP group (1%) were lost to PNF, compared to none in the DCD-NRP-SCS group.

Table 2
Intraoperative parameters and outcomes.

Outcomes	DCD-DP-SCS (n = 59)	DCD-NRP-SCS (n = 101)	DCD-DP-NMP (n = 78)	*P* value
Postreperfusion syndrome	22 (37%)	11 (11%)	12 (15%)	<.001
Surgical duration (min)	425 (360-499)	442 (390-514)	476 (414-547)	.001
Anhepatic phase (min)	51 (46-69)	59 (52-68)	65 (56-83)	<.001
Vasopressor bolus[a]	48 (81%)	73 (72%)	45 (57%)	.009
Vasopressor infusion				
Prereperfusion	34 (58%)	69 (68%)	53 (68%)	.336
Postreperfusion	36 (61%)	61 (60%)	57 (73%)	.168
Potassium (mmol/L)				
Prereperfusion	4.1 (3.8-4.6)	4.1 (3.8-4.6)	4.1 (3.9-4.4)	.921
Postreperfusion	5.5 (4.8-6.3)	4.9 (4.2-5.8)	4.8 (4.2-5.5)	.002
ΔK	1.4 (0.8-1.8)	0.8 (0.3-1.6)	0.6 (0.1-1.2)	<.001
Insulin usage				
Prereperfusion	15 (25%)	29 (29%)	22 (28%)	.915
Postreperfusion	7 (12%)	11 (11%)	9 (12%)	>.999
Lactate (mmol/L)				
Prereperfusion	2.4 (2.0-3.3)	2.3 (1.8-3.0)	2.6 (1.8-3.1)	.390
Peak postreperfusion[b]	3.8 (3.1-5.0)	3.2 (2.3-3.8)	3.6 (3.0-4.5)	<.001
Calcium (mmol/L)				
Prereperfusion	1.2 (1.1-1.2)	1.2 (1.1-1.3)	1.1 (1.0-1.2)	<.001
Postreperfusion	1.3 (1.2-1.4)	1.3 (1.2-1.4)	1.3 (1.2-1.4)	.407
Total blood loss (L)	3.9 (2.5-7.2)	4.6 (2.9-7.3)	6.0 (3.5-8.9)	.062
Concentrated red cell units				
Total	4 (1-7)	4 (2-8)	5 (2-8)	.452
Postreperfusion	2 (0-4)	2 (0-3)	2 (0-4)	.996
Fresh frozen plasma units				
Total	0 (0-4)	4 (0-4)	4 (1-6)	.003

(*continued on next page*)

Table 2 (*continued*)

Outcomes	DCD-DP-SCS (n = 59)	DCD-NRP-SCS (n = 101)	DCD-DP-NMP (n = 78)	*P* value
Postreperfusion	0 (0-2)	2 (0-4)	2 (0-4)	.055
Platelets units				
Total	0 (0-1)	1 (0-2)	1 (0-2)	.223
Postreperfusion	0 (0-1)	1 (0-1)	0 (0-1)	.478
Cryoprecipitate units				
Total	0 (0-2)	1 (0-2)	2 (0-4)	.014
Postreperfusion	0 (0-2)	1 (0-2)	0 (0-2)	.131
Tranexamic acid (g)				
Total	0 (0-2)	1 (0-1)	1 (0-2)	.862
Postreperfusion	0 (0-1)	0 (0-1)	0 (0-0)	.691

Data presented as median (IQR) or number (%).
Anhepatic phase: native liver explant to reperfusion of donor liver.
DCD, donation after circulatory death; DP, direct procurement; NMP, ex situ normothermic machine perfusion; NRP, in situ normothermic regional perfusion; SCS, static cold storage; ΔK, plasma potassium change (increase) at reperfusion.

[a] Within 5 min of reperfusion.

[b] Within 8 h of reperfusion.

3.4. Analysis of patients with PRS

Early transplant outcomes (Table 3) in patients who developed PRS were further compared with those who did not. Occurrence of PRS was associated with increased AKI and frequency of renal replacement therapy, and greater peak ALT and MEAF score. Recipients with PRS had a significantly longer ICU stay. Logistic regression to identify factors independently associated with PRS (Table 4) showed that recipient age (OR 1.10, 95% CI 1.05-1.17, $P < .001$), and liver treatment method were significant predictors for PRS (Reference DCD-DP-SCS: DCD-NRP-SCS OR 0.16, 95% CI 0.06-0.39, $P < .001$; DCD-DP-NMP OR 0.38, 95% CI 0.15-0.91, $P = .032$).

3.5. Transplant survival

The median follow-up of DCD-DP-SCS, DCD-NRP-SCS, and DCD-DP-NMP groups are 70 months, 30 months, and 39 months, respectively. The 1-year transplant survival (graft survival, noncensored to death) of DCD-DP-SCS, DCD-NRP-SCS, and DCD-DP-NMP treated livers was 90%, 94%, and 94%, respectively. However, 5-year transplant survival was significantly worse after DCD-DP-SCS (69%) compared to the DCD-NRP-SCS group (85%, Hazard ratio (HR) 2.4, 95% CI 1.1-5.4, $P = .028$). Comparison between DCD-DP-SCS and DCD-DP-NMP was compatible with a similar effect (84%, HR 2.0, 95% CI 0.9-4.4, $P = .089$).

Overall, the 5-year transplant survival (Fig. 2A) was much lower in recipients with PRS vs without (HR 2.9, 95% CI 1.3-6.7; $P = .012$), but not significantly different within study groups (Fig. 2B-D).

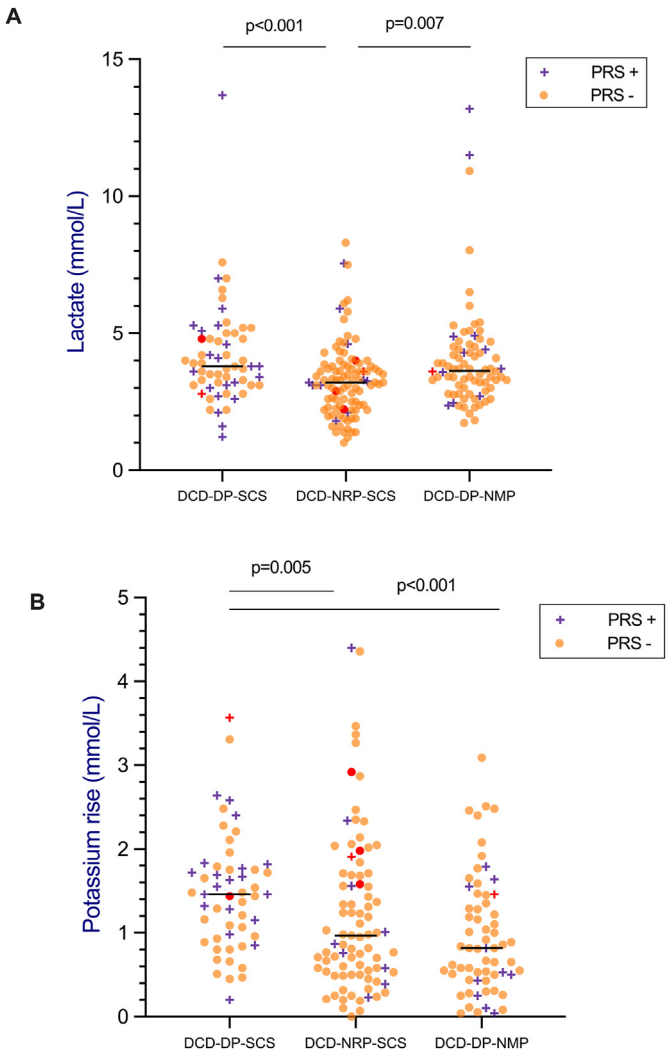

Figure 1. Column scatter plot for postreperfusion lactate and potassium in the 3 groups. Dots represent livers without PRS and the cross represents livers with PRS. Red points represent livers with at least moderate (>30%) macrosteatosis. (A) Peak lactate (mmol/L) after reperfusion; (B) plasma potassium change (increase) (ΔK, mmol/L) at reperfusion. Crossbar at the median. Pairwise comparison: Dunn test. DCD, donation after circulatory death; DP, direct procurement; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; PRS, postreperfusion syndrome; SCS, static cold storage.

4. Discussion

The quality of organs procured from donors after circulatory death, as reflected in perioperative complications, is the main focus of this study. These organs sustain a prolonged period of warm ischemia and tolerate further ischemia and reperfusion poorly. Historically, outcomes achieved through the use of organs from heart-beating donors fulfilling brain death criteria, recovered using static preservation fluid and kept in cold storage, proved far superior to any attempts employing DCD donors. However, as ever-increasing demand exceeded the supply of organs from

Table 3
Outcomes.

Parameter	Liver treatment method				Presence of PRS		
	DCD-DP-SCS (n = 59)	DCD-NRP-SCS (n = 101)	DCD-DP-NMP (n = 78)	*P* value	PRS− (n = 193)	PRS+ (n = 45)	*P* value
Peak ALT (d 1-7)	697 (451-1277)	508 (328-970)	360 (208-621)	<.001	479 (265-807)	743 (328-1277)	.003
MEAF score	5.8 (4.8-7.0)	4.1 (2.8-5.4)	3.3 (2.1-5.2)	<.001	4.1 (2.7-5.7)	5.0 (3.9-6.8)	<.001
PNF	2 (3%)	0	1 (1%)	-	1 (0.5%)	2 (4%)	.093
AKI stage ≥ 2	28 (47%)	29 (29%)	22 (28%)	.033	57 (30%)	22 (49%)	.021
RRT < POD7	9 (15%)	16 (16%)	12 (15%)	>.999	22 (11%)	15 (33%)	<.001
ICU stay	2 (1-4)	3 (2-4)	3 (2-4)	.461	2 (2-4)	3 (2-7)	.039
Hospital stay	16 (13-24)	17 (13-24)	19 (12-28)	.890	17 (13-25)	20 (15-27)	.093

Data presented as median (interquartile ranges) or number (%).
AKI, acute kidney injury; ALT, alanine aminotransferase; DCD, donation after circulatory death; DP, direct procurement; ICU, intensive care unit; MEAF, model for early allograft function; NMP, ex situ normothermic machine perfusion; NRP, in situ normothermic regional perfusion; PNF, primary nonfunction; POD, postoperative day; PRS, postreperfusion syndrome; RRT, renal replacement therapy; SCS, static cold storage.

Table 4
Multivariable logistic regression for PRS[a].

Variables	Adjusted OR	95% CI	*P*
Treatment method			
DCD-DP-SCS	Reference		
DCD-NRP-SCS	0.16	0.06-0.39	<.001
DCD-DP-NMP	0.38	0.15-0.91	.032
Recipient age	1.10	1.05-1.17	<.001

DCD, donation after circulatory death; DP, direct procurement; NMP, ex situ normothermic machine perfusion; NRP, in situ normothermic regional perfusion; OR, odds ratio; PRS, postreperfusion syndrome; SCS, static cold storage.

[a] Logistic regression model with donor age (years), cold ischemia time, recipient age (years), model for end-stage liver disease, liver treatment method, and macrosteatosis >30%.

DBD donors, interest in techniques that might prevent or lessen IR injury and improve DCD outcomes intensified.[3] Our results show that the novel approach of normothermic perfusion of DCD grafts, either with regional perfusion during procurement or with machine perfusion in the preimplantation phase, can improve organ function and yield better recipient outcomes. This series has also shown that machine perfusion remains beneficial even when performed after a significant period of SCS because it was always initiated at the recipient center, not at the site of liver procurement as is preferred practice in many units.

Early experience of DCD liver transplantation suggested a higher risk of the marked hypotension now described as PRS. We selected this as a key outcome because it appeared to be linked to other adverse perioperative outcomes, including EAD, AKI, and longer-term complications.[31-34] Rapid restoration of blood flow to the donor organ generates reactive oxygen species and vasoactive mediators sufficient to cause PRS in 10% to 60% of recipients. It is also associated with plasma potassium increases, as portal vein unclamping releases pooled splanchnic blood and potassium-rich preservation solution into the systemic circulation.[35,36] We hypothesized that the severity of both PRS and hyperkalemia may be related to the severity of ischemic injury sustained during organ procurement and storage and that the use of NRP or NMP to perfuse the donor organ at physiologic temperature and oxygenation could enhance the recovery of metabolic functions and energy substrates, potentially limiting IR injury.[37-39] Moreover, early restoration of circulation by NRP could have a preconditioning effect, inducing resilience to further ischemia. This concept was supported by a propensity-matched investigation reporting much higher rates of PRS and hyperkalemia with DCD vs DBD grafts (25.7% vs 12.3% and 33.8% vs 18.9% respectively, $P < .05$),[5] and a similar study describing a significant increase in vasopressor use and transfusion requirement.[40] Use of machine perfusion to supplement SCS appeared to alter this in a randomized trial demonstrating a marked reduction in PRS in both DBD and DCD grafts,[41] and in a study of exclusively DCD grafts reporting significantly fewer vasopressor infusions.[42] Our report confirms these results in a larger DCD cohort and is the first to evaluate PRS, AKI, graft injury, and other perioperative outcomes during a period of concurrent use of 3 distinct perfusion modalities.

Graft dysfunction associated with IR injury may also present with significant coagulopathy and bleeding, associated with the release of endogenous heparin and plasminogen activator from the graft, sometimes necessitating high-volume transfusion. Improved postreperfusion coagulation profile and reduced transfusion requirements have been reported in nonrandomized comparisons of NMP with SCS in mixed DBD/DCD series.[42,43] However, we did not identify significant differences in total blood loss, nor in all-product transfusion and use of antifibrinolytics following reperfusion in our study, possibly because of reduced statistical power in this DCD-only cohort.

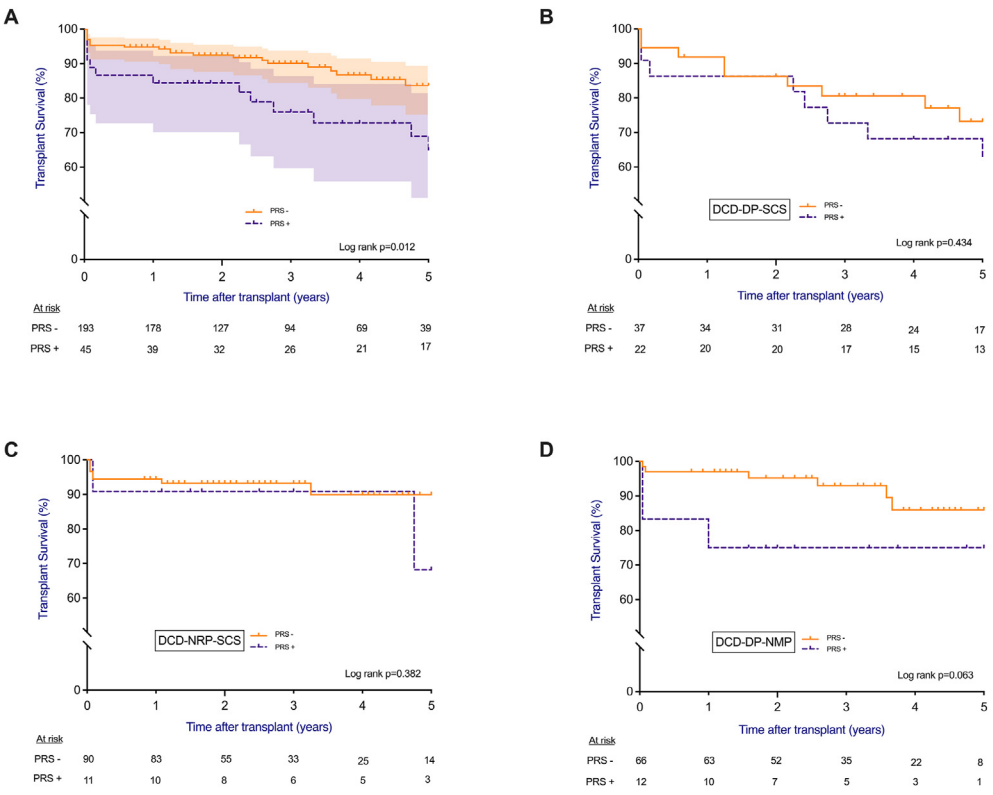

Figure 2. Kaplan-Meier estimates of transplant survival (graft survival, noncensored for death), divided into groups according to the presence of PRS. (A) Overall transplant survival; (B) transplant survival in the DCD-DP-SCS group; (C) transplant survival in the DCD-NRP-SCS group; (D) transplant survival in the DCD-DP-NMP group. DCD, donation after circulatory death; DP, direct procurement; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; PRS, postreperfusion syndrome; SCS, static cold storage.

An increased risk of AKI, potentially from the inflammatory response to IR, has also been associated with DCD grafts, making its prevention an important goal for any donor, graft, or recipient treatment.[6,44] The incidence of AKI with DCD-DP-SCS grafts in our study mirrors previous reports, with reduced AKI in both normothermic perfusion groups despite significantly longer warm ischemia, and higher preoperative creatinine present in the DCD-NRP-SCS group. Moreover, subgroup analysis demonstrated that patients who sustained PRS needed renal replacement therapy more often, a treatment predicting impaired survival.[45,46] We also found that EAD, as identified by peak ALT and MEAF score, was strongly associated with PRS and significantly less frequent in the NRP- and NMP-treated DCD grafts. Although our study was not powered to identify a beneficial effect on longer-term graft and patient outcomes, these results merit further evaluation.

There are a small number of moderate to severe macrosteatotic DCD livers (7/238, 3.0%) in the present study with 43% (n = 3) PRS incidence, but this did not appear as a significant risk factor in adjusted analysis (OR 4.17, 95% CI 0.70-23.6; $P = .101$). The small sample size reflects the anxiety about the use of moderately/severely fatty DCD livers and the present study could not show the influence reported by other larger series. A study from the Mayo Clinic, Florida about the impact of macrosteatosis livers on PRS had similar numbers, 11 liver transplants from moderately macrosteatotic DCD livers over a study period of 17 years.[47] However, in a larger multicenter study by the same Mayo group of hospitals, 3.6% (26/714) liver transplants were recorded from moderate (>30%) macrosteatosis DCD livers over a 10-year period with significantly increased PRS rate (53.9%; $P = .002$).[48] They concluded that both DCD liver graft and moderate macrosteatosis have an additive effect with anticipated higher rates of PRS, PNF, postreperfusion cardiac arrest, EAD, and AKI. Future clinical studies with defatting protocols will answer the utility of normothermic perfusion of fatty livers.[49]

These findings must be qualified by the potential biases and statistical limitations inherent in any single-center retrospective study. In particular, the nonuse of some organs on the basis of biochemical testing during NMP and NRP may have improved graft selection in these groups, a potential benefit of machine perfusion not addressed in this study. On the other hand, the perceived value of perfusion techniques in the DCD setting may have favored use in higher-risk recipients like retransplants and previous surgery. The imperative to minimize ischemia time in DCD livers may have encouraged the use of DCD-DP-SCS organs in recipients with short predicted explant times when NRP and NMP were unavailable. This may explain overrepresentation of females (assigned female at birth) with primary biliary cholangitis, and others with lower surgical risk, in our DCD-DP-SCS group despite similar age and MELD profiles. However, this would likely lead to an underestimation of the effectiveness of these techniques, supporting rather than undermining our conclusions. We acknowledge that the number of patients and events reported in this study did not allow robust statistical modeling. However, we suggest that a number of factors taken together justify confidence in our main results: inclusion of consecutive recipients of all DCD transplants (excluding a small number given grafts preserved with both NRP and NMP or in whom veno-venous bypass was used); equivalence between

groups in most important donor and recipient risk factors; evidence that some recipients at higher surgical risk were selected for normothermic perfusion; protocolized management in all aspects unrelated to liver treatment during the study period; and consistency of benefit across a wide range of surrogate measures and clinical outcomes.

In conclusion, perfusion of livers from DCD donors with either NMP or NRP compared to SCS alone appears to mitigate the effects of IR injury in the perioperative period, as indicated by significantly reduced incidences of PRS, AKI, and EAD. Importantly, outcomes from NRP remained superior to SCS despite longer donor fWIT, higher preoperative serum creatinine in the recipient, and a relatively higher proportion of retransplants. Moreover, NMP was effective even when implemented after a period of SCS. Future studies may refine or combine NRP and NMP techniques to further reduce ischemia-related injury in DCD liver transplantation, increase the proportion of grafts usable for transplant, improve the selection of marginal grafts, and potentially define a new standard for liver preservation.

Author contributions

A.P., R.G., V.K., and C.W.: Study design, performance of the study, data collection, statistical analysis, interpretation, and manuscript writing.

A.B. and J.K.: Performance of the study, interpretation, and manuscript writing.

L.S., C.F., R.W., A.R., and M.M.: Performance of the study and data collection.

All authors participated in the critical review and approval of the final manuscript.

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Declaration of competing interest

The authors of this manuscript have conflicts of interest to disclose as described by *American Journal of Transplantation*. Andrew Butler holds a share of a patent on the circuit used by the OrganOx metra device. Christopher Watson is a consultant to OrganOx. The other authors have no conflicts of interest to disclose as described by *American Journal of Transplantation*.

Data availability

The data generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2025.01.007.

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References

1. NHS Blood and Transplant. Organ and tissue donation and transplantation. Activity report 2022/23. Accessed January 28, 2024. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/30198/activity-report-2022-2023-final.pdf.
2. Kwong AJ, Kim WR, Lake JR, et al. OPTN/SRTR 2019 annual data report: liver. *Am J Transplant*. 2021;21(Suppl 2):208–315. https://doi.org/10.1111/ajt.16494.
3. Watson CJE, Dark JH. Organ transplantation: historical perspective and current practice. *Br J Anaesth*. 2012;108(Suppl 1):i29–i42. https://doi.org/10.1093/bja/aer384.
4. Abbas SH, Friend PJ. Principles and current status of abdominal organ preservation for transplantation. *Surg Pract Sci*. 2020;3:100020. https://doi.org/10.1016/j.sipas.2020.100020.
5. Pan X, Apinyachon W, Xia W, et al. Perioperative complications in liver transplantation using donation after cardiac death grafts: a propensity-matched study. *Liver Transpl*. 2014;20(7):823–830. https://doi.org/10.1002/lt.23888.
6. Leithead JA, Tariciotti L, Gunson B, et al. Donation after cardiac death liver transplant recipients have an increased frequency of acute kidney injury. *Am J Transplant*. 2012;12(4):965–975. https://doi.org/10.1111/j.1600-6143.2011.03894.x.
7. Lee DD, Singh A, Burns JM, Perry DK, Nguyen JH, Taner CB. Early allograft dysfunction in liver transplantation with donation after cardiac death donors results in inferior survival. *Liver Transpl*. 2014;20(12):1447–1453. https://doi.org/10.1002/lt.23985.
8. Friend PJ. Strategies in organ preservation-a new golden age. *Transplantation*. 2020;104(9):1753–1755. https://doi.org/10.1097/TP.0000000000003397.
9. Moers C, Leuvenink HGD. Changing the organ preservation game. *Transplantation*. 2020;104(5):895–896. https://doi.org/10.1097/TP.0000000000003076.
10. Petrenko A, Carnevale M, Somov A, et al. Organ preservation into the 2020s: the era of dynamic intervention. *Transfus Med Hemother*. 2019;46(3):151–172. https://doi.org/10.1159/000499610.
11. Watson CJE, Gaurav R, Butler AJ. Current techniques and indications for machine perfusion and regional perfusion in deceased donor liver transplantation. *J Clin Exp Hepatol*. 2024;14(2):101309. https://doi.org/10.1016/j.jceh.2023.101309.
12. National Institute for Health and Care Excellence (NICE). Ex-situ machine perfusion for extracorporeal preservation of livers for transplantation. *Interventional procedure guideline*; January 16, 2019. https://www.nice.org.uk/guidance/ipg636. Accessed March 20, 2024.
13. Bakhtiyar SS, Maksimuk TE, Pomposelli JJ, Pomfret EA, Hoffman JRH. Unifying the lexicon: a call to standardize organ donation terminologies.

Am J Transplant. 2024;24(10):1913–1915. https://doi.org/10.1016/j.ajt.2024.07.004.
14. Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant*. 2006;6(4):783–790. https://doi.org/10.1111/j.1600-6143.2006.01242.x.
15. O'Neill S, Asgari E, Callaghan C, et al. The British Transplantation Society guidelines on organ donation from deceased donors after circulatory death. *Transplant Rev (Orlando)*. 2023;37(4):100791. https://doi.org/10.1016/j.trre.2023.100791.
16. Barber K, Madden S, Allen J, et al. Elective liver transplant list mortality: development of a United Kingdom end-stage liver disease score. *Transplantation*. 2011;92(4):469–476. https://doi.org/10.1097/TP.0b013e318225db4d.
17. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003;124(1):91–96. https://doi.org/10.1053/gast.2003.50016.
18. Aggarwal S, Kang Y, Freeman JA, Fortunato FL, Pinsky MR. Postreperfusion syndrome: hypotension after reperfusion of the transplanted liver. *J Crit Care*. 1993;8(3):154–160. https://doi.org/10.1016/0883-9441(93)90021-c.
19. Siniscalchi A, Gamberini L, Bardi T, et al. Post-reperfusion syndrome during orthotopic liver transplantation, which definition best predicts postoperative graft failure and recipient mortality? *J Crit Care*. 2017;41:156–160. https://doi.org/10.1016/J.JCRC.2017.05.020.
20. KDIGO board members. *Kidney Int Suppl*. 2011;2012:2–3. https://doi.org/10.1038/kisup.2012.3.
21. Pareja E, Cortes M, Hervás D, et al. A score model for the continuous grading of early allograft dysfunction severity. *Liver Transpl*. 2015;21(1):38–46. https://doi.org/10.1002/lt.23990.
22. Zalewska K, Ploeg R. National standards for organ retrieval from deceased donors. *NHS Blood and Transplant*; 2013. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12548/mpd1043-nors-standard.pdf. Accessed December 23, 2023.
23. Butler AJ, Randle LV, Watson CJE. Normothermic regional perfusion for donation after circulatory death without prior heparinization. *Transplantation*. 2014;97(12):1272–1278. https://doi.org/10.1097/TP.0000000000000082.
24. Watson CJE, Hunt F, Messer S, et al. In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. *Am J Transplant*. 2019;19(6):1745–1758. https://doi.org/10.1111/ajt.15241.
25. Watson CJE, Jochmans I. From "gut feeling" to objectivity: machine preservation of the liver as a tool to assess organ viability. *Curr Transplant Rep*. 2018;5(1):72–81. https://doi.org/10.1007/s40472-018-0178-9.
26. Watson CJE, Kosmoliaptsis V, Pley C, et al. Observations on the ex situ perfusion of livers for transplantation. *Am J Transplant*. 2018;18(8):2005–2020. https://doi.org/10.1111/ajt.14687.
27. Watson CJE, Gaurav R, Fear C, et al. Predicting early allograft function after normothermic machine perfusion. *Transplantation*. 2022;106(12):2391–2398. https://doi.org/10.1097/TP.0000000000004263.
28. Gaurav R, Butler AJ, Kosmoliaptsis V, et al. Liver transplantation outcomes from controlled circulatory death donors: SCS vs in situ NRP vs ex situ NMP. *Ann Surg*. 2022;275(6):1156–1164. https://doi.org/10.1097/SLA.0000000000005428.
29. Watson C. UK national NRP Protocol UK protocol for normothermic regional perfusion (NRP) in controlled donation after circulatory determination of death NRP National Protocol. 2023. Accessed January 28, 2024. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/29700/uk-protocol-for-normothermic-regional-perfusion-version-110-28-04-2023.pdf.
30. Bral M, Dajani K, Leon Izquierdo D, et al. A back-to-base experience of human normothermic ex situ liver perfusion: does the chill kill? *Liver Transpl*. 2019;25(6):848–858. https://doi.org/10.1002/lt.25464.
31. Manning MW, Kumar PA, Maheshwari K, Arora H. Post-reperfusion syndrome in liver transplantation-an overview. *J Cardiothorac Vasc Anesth*. 2020;34(2):501–511. https://doi.org/10.1053/j.jvca.2019.02.050.
32. Siniscalchi A, Gamberini L, Laici C, et al. Post reperfusion syndrome during liver transplantation: from pathophysiology to therapy and preventive strategies. *World J Gastroenterol*. 2016;22(4):1551–1569. https://doi.org/10.3748/wjg.v22.I4.1551.
33. Paugam-Burtz C, Kavafyan J, Merckx P, et al. Postreperfusion syndrome during liver transplantation for cirrhosis: outcome and predictors. *Liver Transpl*. 2009;15(5):522–529. https://doi.org/10.1002/lt.21730.
34. Sahmeddini MA, Tehran SG, Khosravi MB, et al. Risk factors of the post-reperfusion syndrome during orthotopic liver transplantation: a clinical observational study. *BMC Anesthesiol*. 2022;22(1):89. https://doi.org/10.1186/S12871-022-01635-3.
35. Patrono D, Romagnoli R. Postreperfusion syndrome, hyperkalemia and machine perfusion in liver transplantation. *Transl Gastroenterol Hepatol*. 2019;4:68. https://doi.org/10.21037/TGH.2019.08.12.
36. Weinberg L, Lee DK, Koshy AN, et al. Potassium levels after liver reperfusion in adult patients undergoing cadaveric liver transplantation: a retrospective cohort study. *Ann Med Surg (Lond)*. 2020;55:111–118. https://doi.org/10.1016/j.amsu.2020.05.002.
37. Van De Leemkolk FEM, Schurink IJ, Dekkers OM, et al. Abdominal normothermic regional perfusion in donation after circulatory death: a systematic review and critical appraisal. *Transplantation*. 2020;104(9):1776–1791. https://doi.org/10.1097/TP.0000000000003345.
38. Serifis N, Matheson R, Cloonan D, Rickert CG, Markmann JF, Coe TM. Machine perfusion of the liver: a review of clinical trials. *Front Surg*. 2021;8:625394. https://doi.org/10.3389/fsurg.2021.625394.
39. Jia J, Nie Y, Li J, et al. A systematic review and meta-analysis of machine perfusion vs. static cold storage of liver allografts on liver transplantation outcomes: the future direction of graft preservation. *Front Med (Lausanne)*. 2020;7:135. https://doi.org/10.3389/fmed.2020.00135.
40. Chadha RM, Croome KP, Aniskevich S, et al. Intraoperative events in liver transplantation using donation after circulatory death donors. *Liver Transpl*. 2019;25(12):1833–1840. https://doi.org/10.1002/lt.25643.
41. Nasralla D, Coussios CC, Mergental H, et al. A randomized trial of normothermic preservation in liver transplantation. *Nature*. 2018;557(7703):50–56. https://doi.org/10.1038/s41586-018-0047-9.
42. Angelico R, Perera MTPR, Ravikumar R, et al. Normothermic machine perfusion of deceased donor liver grafts is associated with improved postreperfusion hemodynamics. *Transplant Direct*. 2016;2(9):e97. https://doi.org/10.1097/TXD.0000000000000611.
43. Ionescu M-I, Tillakaratne S, Hodson J, et al. Normothermic machine perfusion enhances intraoperative hepatocellular synthetic capacity: a propensity score-matched analysis. *Transplantation*. 2019;103(7):e198–e207. https://doi.org/10.1097/TP.0000000000002720.
44. Umbro I, Tinti F, Scalera I, et al. Acute kidney injury and post-reperfusion syndrome in liver transplantation. *World J Gastroenterol*. 2016;22(42):9314–9323. https://doi.org/10.3748/wjg.v22.i42.9314.
45. Feldkamp T, Bienholz A, Paul A, Saner FH. Renal damage after liver transplantation. *Biosci Rep*. 2020;40(1):BSR20191187. https://doi.org/10.1042/BSR20191187.
46. Sanchez EQ, Gonwa TA, Levy MF, et al. Preoperative and perioperative predictors of the need for renal replacement therapy after orthotopic liver transplantation. *Transplantation*. 2004;78(7):1048–1054. https://doi.org/10.1097/01.tp.0000137176.95730.5b.
47. Croome KP, Lee DD, Croome S, et al. The impact of postreperfusion syndrome during liver transplantation using livers with significant macrosteatosis. *Am J Transplant*. 2019;19(9):2550–2559. https://doi.org/10.1111/ajt.15330.
48. Croome KP, Mathur AK, Mao S, et al. Perioperative and long-term outcomes of utilizing donation after circulatory death liver grafts with macrosteatosis: a multicenter analysis. *Am J Transplant*. 2020;20(9):2449–2456. https://doi.org/10.1111/ajt.15877.
49. Abbas SH, Ceresa CDL, Hodson L, et al. Defatting of donor transplant livers during normothermic perfusion-a randomised clinical trial: study protocol for the DeFat study. *Trials*. 2024;25(1):386. https://doi.org/10.1186/s13063-024-08189-4.